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Published in:
Psychiatry Investigation

DOI:
10.4306/pi.2017.14.5.687

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

ORIGINAL ARTICLE
https://doi.org/10.4306/pi.2017.14.5.687

Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Genome-Wide Supported Risk Variants in *MIR137*, *CACNA1C*, *CSMD1*, *DRD2*, and *GRM3* Contribute to Schizophrenia Susceptibility in Pakistani Population

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Objective Schizophrenia is a chronic neuropsychiatric disease afflicting around 1.1% of the population worldwide. Recently, *MIR137*, *CACNA1C*, *CSMD1*, *DRD2*, and *GRM3* have been reported as the most robustly emerging candidates involved in the etiology of schizophrenia. In this case control study, we performed an association analysis of rs1625579 (*MIR137*), rs1006737, rs4765905 (*CACNA1C*), rs10503253 (*CSMD1*), rs1076560 (*DRD2*), rs12704290, rs6465084, and rs148754219 (*GRM3*) in Pakistani population.

Methods Schizophrenia was diagnosed on the basis of the Diagnostic and Statistical Manual of Mental Disorders 4th ed (DSM-IV). Detailed clinical information, family history of all patients and healthy controls were collected. RFLP based case control association study was performed in a Pakistani cohort of 508 schizophrenia patients and 300 healthy control subjects. Alleles and genotype frequencies were calculated using SPSS.

Results A significant difference in the genotype and allele frequencies for rs4765905, rs1076560 and rs6465084 were found between the patients and controls (p=0.000).

Conclusion This study provides substantial evidence supporting the role of *CACNA1C*, *GRM3* and *DRD2* as schizophrenia susceptibility genes in Pakistani population.
Psychiatry Investig 2017;14(5):687-692

Key Words Schizophrenia, *MIR137*, *CACNA1C*, *CSMD1*, *GRM3*, *DRD2*, Pakistan.

INTRODUCTION

Elucidation of etiological factors of schizophrenia remains a major challenge for researchers. In the last two decades several Genome Wide Association Studies (GWAS) have been performed to unravel genetic causes of the disease.[1-3] Simultaneously, hundreds or even thousands of single nucleotide polymorphisms (SNPs) were reported, which individually could explain only a small fraction of the genetic contribution to the disease; however, cumulative effect of these risk variants may offer a larger share in genetic architecture of disease.[4]

The Schizophrenia Psychiatric GWAS Consortium (PGC) has recently reported the largest schizophrenia genome-wide association study comprising 36,989 cases and 113,075 controls. This study revealed 108 loci with genome-wide significance, including 83 previously reported loci.[3] In the present study we selected a set of statistically top schizophrenia genes, *MIR137* and two of its putative targets (*CACNA1C* and *CSMD1*) along with potential therapeutic targets of schizophrenia *DRD2* and *GRM3* from the above report.

MIR137 encodes microRNA (miR-137), a well-known regulator of adult neurogenesis,[5] which is one of the risk genes involved in the etiology of range of neuropsychiatric disorders.[2,3] A number of GWAS revealed rs1625579 (located within intron

Received: July 4, 2016 **Revised:** August 22, 2016
Accepted: September 26, 2016 **Available online:** June 16, 2017

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of *MIR137*) indicating robust association with schizophrenia.[2,6,7] *CACNA1C* encodes the alpha 1C subunit of the L-type voltage-gated calcium channel and variations in it have consistently been reported as a potential risk factor for schizophrenia, bipolar and major depressive disorders.[8-10] Several genetic association studies have identified *CACNA1C* intronic SNPs rs1006737 (A-allele) and rs4765905 (C allele) as risk factors for schizophrenia.[2,11,12] *CSMD1*, the CUB and Sushi multiple domains-1 is a susceptibility gene for schizophrenia and multiple neurodevelopmental disorders.[13,14] The SNP rs10503253 (A allele), located within *CSMD1* gene has been reported to be a risk factor for schizophrenia.[15,16]

Glutamate is most abundant excitatory neurotransmitter in the central nervous system (CNS). Glutamate neurotransmission is essential for several brain functions such as learning, memory, cognition, neural development and motor control. Furthermore, glutamate neurotransmitter hypofunction might be involved in pathophysiology of schizophrenia. *GRM3* (type-3 metabotropic glutamate receptor) encodes the mGluR3 which regulates glutamate neurotransmission and synaptic plasticity. The functional polymorphism rs6465084 (*GRM3*) has been found to be associated with poor performance of cognitive function in schizophrenia.[17,18] Recently, rs12704290 and rs148754219 in *GRM3* have gained much attention as schizophrenia risk variants.[3,19]

The Dopamine hypothesis is the oldest theory proposing that impairments in dopamine neurotransmission systems are involved in pathophysiology of schizophrenia. The dopamine receptor type 2 (*DRD2*) is associated with schizophrenia as well as highlighted as a potential drug target of schizophrenia. Moreover, genetic variation within *DRD2* is associated with schizophrenia at genome-wide significance level.[3,20] The functional SNP rs1076560 in *DRD2* gene is one of the known risk variants for schizophrenia.[21]

There is no data available on the prevalence of schizophrenia in the Pakistani population mainly due to low literacy, lack of disease awareness and various social taboos related to psychiatry disorders. No study has so far been conducted to see whether *MIR137*, *CACNA1C*, *CSMD1*, *DRD2* and *GRM3* confer a risk for schizophrenia in Pakistani population. Based on the reported evidence from several GWAS, we selected the top eight SNPs from the above reported genes to study their association with schizophrenia in Pakistani population.

METHODS

Subjects

This study was approved by the local research ethics committee of the National Institute for Biotechnology and Genetic Engineering (NIBGE), Faisalabad, Pakistan. All the subjects, both control and patients enrolled for this study were of Pakistani descend. This study included 508 unrelated patients with schizophrenia comprising of 382 men and 126 women with a mean age of 46 years and 300 unrelated healthy controls comprising of 175 men and 125 women, with a mean age of 44 years. Informed written consent was obtained from all the subjects or their legal guardians after explaining this study in their native language. Schizophrenia was diagnosed on the basis of clinical history and symptoms based on the Diagnostic and Statistical Manual of Mental Disorders 4th ed (DSM-IV). All the patients were examined and diagnosed independently by at least two psychiatrists from local hospitals

SNP selection

The largest schizophrenia genome-wide association study of 36,989 cases and 113,075 controls has revealed 108 loci with genome-wide significance.[3] We selected a set of statistically top hits; *MIR137* and two of its putative targets (*CACNA1C* and *CSMD1*) and potential drugs' targets of schizophrenia *DRD2* and *GRM3* from this study. After a thorough literature review of research published prior to January 2015, a total of eight risk SNPs (rs1625579, rs1006737, rs4765905, rs10503253, rs1076560, rs12704290, rs6465084, and rs148754219) were chosen for analysis. Selected SNPs have shown significant positive association (MAF >0.05) with schizophrenia in multiple populations.

Genotyping

In this study, we adopted a case-control approach to test the hypothesis that these risk alleles are associated with schizophrenia in Pakistani population. Genomic DNA was extracted from peripheral blood according to standard organic protocols. Mismatch primers were designed for Restriction Fragment Length Polymorphism (RFLP) (Table 1). For genotyping polymerase chain reaction (PCR) was performed in a total volume of 10 μL containing 50 ng of genomic DNA, 10X key buffer (VWR) 1 μL, 2.5 mM of dNTP-Mix, 10 pmol of each primer, 0.15 μL of ampli-Taq DNA polymerase (VWR) and nuclease-free water. The reaction was performed under following cycling condition: initial denaturation at 95°C for 5 min, 40 cycles of 95°C for 15 sec, 58°C and 72°C for 30 and 45 sec respectively and final extension for 5 min at 72°C. Amplification was visualized using 1% agarose gel and amplicons were digested overnight at 37°C with appropriate enzymes. Finally digested product was resolved on 2% agarose gel for genotyping. Randomly selected PCR products were sequenced on an ABI 3130XL genetic analyzer (Applied Biosystems) using BigDye Terminator v. 3.1 Cycle Sequencing Kit (Applied Biosystems) to verify the RFLP results.

Table 1. Primers sequence and restriction enzymes used for genotyping of SNPs

Gene	SNP	Primer forward	Primer reverse	Product size	Restriction enzyme
MIR137	rs1625579	GAGAACATCATGGGGTCACTAT	CAGTAAAACAAGGGAAATGTTAATCACAAGTA	167bp	RsaI
CACNA1C	rs1006737	TACATAAGTTCCATTCCATCTCAGCCCGGA	GAGCTTGCTGGACCTGAGATT	183bp	XmnI
CACNA1C	rs4765905	GGTGGATGCTGGTTGCAGAC	AGATGTGTCTTCACACATCACAGACCCCGA	169bp	AvaI
CSMD1	rs10503253	AGCAGGTTCAACAGACTTATTTC	TCAGAGAAAGCCCTAGTCCC	221bp	MseI
DRD2	rs1076560	GAGCATCTCCATCTCCAGCT	GTGCAGGTACCCATGAAGTG	499bp	Hph1
GRM3	rS12704290	TGATTTCCTGGGCTGGGA	GTGTCTTTGCCTATGAGCCT	770bp	BseRI
GRM3	rs6465084	CAAAGTTCTCTTTCCAAATTACCATTACAT	CTGCTAATTAGAAAGGTAATCTGTG	201bp	NdeI
GRM3	rs148754219	CAGGAAGCTGCGCGCACAA	CCTCCTCTGGGACCCTTA	218bp	BtsCI

SNP: Single Nucleotide Polymorphism, bp: base pair

Statistical analysis

The allele and genotype frequency analysis were conducted using SPSS version 20 (IBM Corp., Armonk, NY, USA). To check the significance of genotype and allele frequencies in cases and control group; chi-square analysis was used. The odds ratios were also calculated to see the effect of different groups on alleles in SNPs.

RESULTS

A total of eight SNPs were genotyped in 808 samples including 508 patients and 300 controls. Allelic and genotyping frequencies including odds ratios for these eight SNPs in patients and controls are described in Table 2.

In the genotype and allele frequencies of rs4765905, rs1076560 and rs6465084a significant difference was found between patients and control group (p=0.000) (Table 2). The remaining SNPs did not show any significant difference between schizophrenia patients and control group (Table 2). To examine whether the patients' age of onset in schizophrenia has any association with these variants, we split the patients' data set into two groups, one with the onset of disease before 25 years and second after 25 years of age. The data was analysed as described above, only rs6465084 was found associated with age of onset before 25 years (Table 3).

DISCUSSION

In this study, we conducted the first Pakistani population based genetic association of top schizophrenia candidates *MIR137*, *CACNA1C*, *CSMD*, *DRD3*, and *GRM3*. *CACNA1C* (12p13.3) encodes α-1C subunit of the L-type voltage-gated calcium channel, which has been reported to be strongly associated with schizophrenia in several association studies.[2,8,10,22] *CACNA1C* play an important role in development of central nervous system, associated with poor executive function and especially exhibit a profound reduction of bilateral hippocampal activation that leads to impaired memory function.[23,24] In a recent GWAS of schizophrenia, one of the top statistical hit was rs4765905 located within *CACNA1C*.[2] In the present study, the SNP rs4765905 showed significant allelic and genotypic association of risk allele C with schizophrenia (Table 2). Hamshere and colleagues[8] combined additional samples to the analysis performed by Ripke et al.[2] and replicated genome wide significant association of rs4765905 with schizophrenia. A recent cross population study revealed significant association of rs4765905 with schizophrenia (p=0.013999) in Han Chinese samples providing more support to the earlier findings.[12] This positive association of rs4765905 with schizophrenia in Pakistani subjects depicted in the present study pro-

Table 2. Allele and genotype frequency of SNPs association analysis in patients vs. controls

Gene	SNP/position	Allele frequency (%)		p value	Genotype frequency (%)			p value	OR/95% CI
MIR137	rs1625579	T	G	0.137	TT	TG	GG	0.192	1.21 (0.94−1.54)
	SCZ	774 (79.79)	196 (20.21)		378 (77.9)	18 (3.7%)	89 (18.4)		
	CTR	452 (76.61)	138 (23.39)		223 (75.6)	6 (2.0)	66 (22.4)		
CACNA1C	rs1006737	G	A	0.935	GG	GA	AA	0.885	0.99 (0.72−1.35)
	SCZ	870 (88.06)	118 (11.94)		393 (79.6)	84 (17.0)	17 (3.4)		
	CTR	524 (87.92)	72 (12.08)		235 (78.9)	54 (18.1)	9 (3.0)		
CACNA1C	rs4765905	G	C	0.000	GG	GC	CC	0.000	2.58 (1.87−3.56)
	SCZ	769 (79.61)	197 (20.39)		310 (64.2)	149 (30.8)	24 (5.0)		
	CTR	544 (90.97)	54 (9.03)		254 (84.9)	36 (12.0)	9 (3.0)		
CSMD1	rs10503253	C	A	0.607	CC	CA	AA	0.238	0.94 (0.75−1.18)
	SCZ	745 (73.62)	267 (26.38)		284 (56.1)	177 (35.0)	45 (8.9)		
	CTR	423 (72.43)	161 (27.57)		152 (52.1)	119 (40.8)	21 (7.2)		
DRD2	rs1076560	C	A	0.000	CC	CA	AA	0.00	1.77 (1.40−2.24)
	SCZ	467 (77.83)	133 (22.17)		189 (37.6)	295 (58.6)	19 (3.8)		
	CTR	673 (66.90)	333 (33.1)		174 (58.0)	119 (39.7)	7 (2.3)		
GRM3	rs12704290	G	A	0.084	GG	GA	AA	0.21	0.56 (0.26−1.10)
	SCZ	979 (96.93)	31 (3.07)		478 (94.7)	23 (4.6)	4 (0.8)		
	CTR	590 (98.33)	10 (1.67)		290 (96.7)	10 (3.3)	0 (0.0)		
GRM3	Rs6465084	G	A	0.000	GG	GA	AA	0.00	0.69 (0.54−0.82)
	SCZ	473 (50.97)	455 (49.03)		64 (13.8)	345 (74.4)	55 (11.9)		
	CTR	246 (41)	354 (59)		12 (4.0)	222 (74.0)	66 (22.0)		
GRM3	rs114875219	G	A	0.000	GG	GA	AA	0.24	0.49 (0.21−1.13)
	SCZ	986 (97.62)	24 (2.38)		482 (95.4)	22 (4.4)	1 (0.2)		
	CTR	593 (98.83)	7 (1.17)		293 (97.7)	7 (2.3)	0 (0.0)		

SNP: Single Nucleotide Polymorphism

vides additional evidence to support the role of *CACNA1C* in schizophrenia susceptibility. Several GWAS reported another variant rs1006737 in *CACNA1C* gene associated with schizophrenia. Allele A of rs1006737 has been reported to be more consistently associated with schizophrenia as a risk allele in several GWAS followed by functional studies.[2,8,23,25,26] We did not find genetic association of risk allele A among the patients recruited in this study. Negative association of rs1006737 with schizophrenia has also been reported in studies conducted on Chinese and Japanese patients.[27,28] The negative association in the current study might be due to relatively small sample size or the frequency of the risk A-allele considerably lower in samples of Asian origin than in Caucasian as discussed by Hori and colleagues.[28]

The functional variant rs1076560 in *DRD2* gene affects the balance of expression from D2S (D2 short isoform) to D2L (D2 long isoform), which in turn influences the dopaminergic signalling. The risk allele (T) of rs1076560 decreases expression of the *DRD2* short D2 isoform, affects the brain activity and connectivity during emotion processing.[29] This allele was associated with impairments in decision-making and behavioural effects of schizophrenia patients.[30] There is a strong evidence that this variant increases the risk of psychosis-related phenotypes, including schizophrenia.[27,31] The positive association of rs1076560 in Pakistani samples (p=0.000) contributes further in support of existing evidence on the role of this SNP in predisposition to schizophrenia.

The type-3 metabotropic glutamate receptor gene (*GRM3*) is a candidate gene as well as one of the potential therapeutic targets for schizophrenia.[3] In this study we found a significant association of allele A and genotype AA of rs6465084 with schizophrenia patients. These results are in line with previous studies, which reported that functional polymorphism rs6465084 (*GRM3*) has been found associated with poor performance cognitive function of schizophrenia.[3,17] In the present study, we could not find any significant differences in genotype and allele frequencies of rs1625579, rs1006737, rs10503253, rs12704290 and rs148754219 between patients and controls. Our results are in agreement with some other studies that reported negative association of these SNPs with schizophrenia.[32-34]

Our second hypothesis was that these risk alleles are associated with age of disease onset; to test this we divided our patients into two cohorts; the group with disease onset before 25 years and that with after 25 years. In this analysis we found a significant association of rs6465084 with age of onset before 25 years (Table 3). These results provide additional indi-

Table 3. Age of onset based association analysis of all SNPs

Gene	SNP/position	Allele frequency (%)		p value	Genotype frequency (%)			p value	OR/95% CI
MIR137	rs1625579	T	G	0.03	TT	TG	GG	0.253	1.21 (0.94−1.54)
	AAO<25	465 (82.16)	101 (17.84)		228 (80.6)	9 (3.2)	46 (16.3)		
	AAO>25	309 (76.49)	95 (23.51)		150 (74.3)	9 (4.5)	43 (21.3)		
CACNA1C	rs1006737	G	A	0.188	GG	GA	AA	0.473	0.99 (0.72−1.35)
	AAO<25	490 (86.88)	74 (13.12)		219 (77.7)	52 (18.4)	11 (3.9)		
	AAO>25	380 (89.62)	44 (10.38)		174 (82.1)	32 (15.1)	6 (2.8)		
CACNA1C	rs4765905	G	C	0.359	GG	GC	CC	0.668	2.58 (1.87−3.56)
	AAO<25	461 (80.59)	111 (19.41)		188 (65.7)	85 (29.7)	13 (4.5)		
	AAO>25	308 (78.17)	86 (21.23)		122 (61.9)	64 (32.5)	11 (5.6)		
CSMD1	rs10503253	C	A	0.341	CC	CA	AA	0.509	0.94 (0.75−1.18)
	AAO<25	460 (74.68)	156 (25.32)		179 (58.1)	102 (33.1)	27 (8.8)		
	AAO>25	285 (71.97)	111 (28.03)		105 (53.0)	75 (37.9)	18 (9.1)		
DRD2	rs1076560	G	A	0.85	GG	GA	AA	0.29	1.77 (1.40−2.24)
	AAO<25	390 (67.47)	188 (32.53)		112 (38.8)	166 (57.4)	11 (3.8)		
	AAO>25	234 (66.86)	116 (33.14)		62 (35.4)	110 (62.9)	03 (1.7)		
GRM3	rs12704290	G	A	0.03	GG	GA	AA	0.09	0.56 (0.26−1.10)
	AAO<25	562 (96.56)	20 (3.44)		274 (94.2)	14 (4.8)	3 (1.0)		
	AAO>25	346 (98.86)	4 (1.14)		172 (98.3)	02 (1.1)	01 (0.6)		
GRM3	rs6465084	G	A	0.000	GG	GA	AA	0.00	0.69 (0.54−0.82)
	AAO<25	473 (50.97)	455 (49.03)		64 (13.8)	345 (74.4)	55 (11.9)		
	AAO>25	246 (41)	354 (59)		12 (4.0)	222 (74.0)	66 (22.0)		
GRM3	rs114875219	G	A	0.09	GG	GA	AA	0.19	0.49 (0.21−1.13)
	AAO<25	571 (98.11)	11 (1.89)		280 (96.2)	11 (3.8)	0 (0.0)		
	AAO>25	337 (96.29)	13 (3.71)		163 (93.1)	11 (6.3)	01 (0.6)		

SNP: Single Nucleotide Polymorphism, AAO: Average Age of Onset

cation that genetic variants significantly contribute to the age of onset in individuals with schizophrenia. There was no significant association between remaining risk variants and age of onset, whereas only rs1625579 and rs12704290 showed significant allelic frequency (p=0.03) between AAO<25 and AAO>25 years (Table 3).

The negative association between schizophrenia and rs1006737, rs1625579, rs10503253, rs12704290, and rs148754219 in our samples probably reflects disease heterogeneity influenced by the ethnic difference. It is also possible that our relatively small sample size for the genetic association study might be the reason for non-significant result.

The *DRD2* and *GRM3* are the most promising targets of effective antipsychotic drugs for treatment of psychiatric disorders specially schizophrenia.[3] Interestingly positive association of rs1076560 (DRD2) and rs6465084 (GRM3) in Pakistani population provides additional line of evidence to the most predominant hypothesis for therapeutic targets for schizophrenia.

In the present study, we found three SNPs (rs4765905, rs1076560 and rs6465084) with significant difference between the patient and control groups (p=0.000). However, rs1625579, rs1006737, rs10503253, rs12704290, and rs148754219 did not show any significant difference between schizophrenia patients and healthy controls. These results provide important evidence for the establishment of rs4765905, rs1076560, and rs6465084as risk variants for schizophrenia in Pakistani population. However, we could not completely exclude the possibility of other variants with schizophrenia susceptibility. Further studies investigating the role of additional causative variants for schizophrenia in Pakistani population are required.

Acknowledgments

We are grateful to all the patients and healthy subjects for their participation in the study. Dr. Imtiaz Dogar Head psychiatry ward DHQ hospital Faisalabad and Imran Murtaza Medical Superintendent of the Fountain House Lahore are thanked for their cooperation in diagnosis of schizophrenia. The Higher Education Commission (HEC) Pakistan financially supported this work.

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